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(21) International Application Number: PCT/US94/10175 (22) International Filing Date: 7 September 1994 (07.09.94) (30) Priority Data: 08/116,908 7 September 1993 (07.09.93) US (71) Applicant: ESCALON OPHTHALMICS, INC. [US/US]; 182 Turnpike Circle, Skillman, NJ 08558 (US). (72) Inventor: BENEDETTO, Dominick, A.; 124 Avenue B, Bayonne, NJ 07002 (US). (74) Agent: SAUNDERS, Thomas, M.; Lorusso & Lord, 440 Commercial Street, Boston, MA 02109 (US).	(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SB). Published <i>With international search report.</i>	
(54) Title: SURFACE ACTIVE VISCOELASTIC SOLUTIONS FOR OCULAR USE (57) Abstract <p>This invention encompasses a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising a pharmaceutical grade viscoelastic fraction selected from a group consisting of an acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms and mixtures of said acyl-substituted hyaluronic acid with hyaluronic acid, and hydroxypropylmethylcellulose. In particular these solutions have a surface tension of between 40 and 65 dynes/cm²; particularly a viscoelastic fraction has an average molecular weight of at least 50,000. In some embodiments a physiological buffer fraction is present. This invention further encompasses a method of using the claimed composition.</p>		

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WO 95/07085

PCT/US94/10175

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SURFACE ACTIVE VISCOELASTIC SOLUTIONS FOR OCULAR USE

This application is a continuation-in-part of copending U.S. Pat. App. 08/061,773 filed May 13, 1993, which is a continuation of U.S. Pat. App. 07/440,078 filed November 22, 1989, now abandoned.

Field of the Invention.

The present invention relates to ophthalmic solutions for use during ocular and intraocular surgery, and more particularly to the use of surface active viscoelastic solutions during the extraction of a cataractous human lens and the implantation of a prosthetic ocular and intraocular lens. During surgery, the use of ophthalmic infusions with controlled physical properties, especially surface activity and viscoelastic properties, is advantageous for (1) replacing the fluid aqueous humor or ocular and intraocular air, (2) protecting the internal structures of the eye from accidental instrument or ocular and intraocular prosthetic device contact, (3) preventing irrigation damage by solutions used in routine cataract surgery, and (4) retarding aspiration from the eye of the viscoelastic solution during the surgical procedure. In addition, the invention relates to a method of adhering a contact lens to the surface of the eye, such as in association with procedures permitting a medical professional to view ocular and intraocular structures through the contact lens and through the viscoelastic solution. In

WO 95/07085

PCT/US94/10175

1 another application, the viscoelastic solution of this invention
2 is used by injecting the solution into or under tissues within
3 the eye, such as to dissect tissue off of the retina.

4 Background of the Invention

5 In the past, biocompatible polymers used in ocular and
6 intraocular surgery have been the naturally occurring
7 mucopolysaccharides hyaluronic acid and chondroitin sulfate;
8 mixtures of hyaluronic acid and chondroitin sulfate; and,
9 cellulose derivatives, such as hydroxypropylmethylcellulose
10 (HPMC). Table 1
11 presents data reported in Viscoelastic Materials, Ed. E.S.
12 Rosen, Proceedings of the Second International Symposium of the
13 Northern Eye Institute, Manchester [U.K.], 17-19 July, 1986
14 (Pergamon Press, New York) as to the molecular weight of
15 commercially available ocular products. Depending on the source
16 from which these mucopolysaccharides are drawn, the molecular
17 weights are estimated in the 50,000 range with the hyaluronic
18 acid extending upwards to the 8×10^6 range. Hyaluronic acid
19 was first isolated and characterized by Meyer, Palmer and
20 reported in the J. Biol. Chem., Vol. 107, p. 629 (1934) and Vol.
21 114, p.689 (1936) and by Balazs in the Fed. Proc. Vol. 17, p.
22 1086 (1958); and chondroitin sulfate by Bray et al. in Biochem.
23 J. Vol. 38, p. 144 (1944); and Patat, Elias, Z. Physiol. Chem.
24 vol. 316, p. 1 (1959).

25
26 Literature in the art describes the basic isolation and
27 characterization of the viscoelastic solutions. It is a
28 surprising feature of this invention which describes the control

WO 95/07085

PCT/US94/10175

1 of viscoelastic properties as related to the surface activity,
2 or the solution fracturing under applied stress. In particular,
3 it is surprising to manipulate or enhance the physical
4 properties of viscoelastic solutions of mucopolysaccharides,
5 hyaluronic acid, and/or chondroitin sulfate. It is believed
6 that disclosure here of a processes to provide hyaluronic acid
7 and species thereof with controlled surface activity is unique.
8 This is also especially true of the control of surface activity
9 of mucopolysaccharide solutions by the addition of biologically
10 compatible surfactants. A characteristic feature of
11 biologically compatible surfactants is the absence of observed
12 alteration in cellular physiology upon contact. Early work in
13 the viscoelastic field was presented by the inventor of this
14 disclosure and his associates. Benedetto, D.A. et. al.,
15 Viscoelastic Materials: Basic Science and Clinical Application,
16 (Symposium Proceedings), University of Manchester, England, July
17 17-19, 1986.

18
19 As to commercial production, a review of the ophthalmic
20 pharmacopoeia reveals there are several viscoelastic solutions
21 produced for ocular and intraocular use during ophthalmic
22 surgery. The most common application for these solutions is in
23 the intraocular lens implant procedure for human cataract
24 surgery. This procedure involves extraction of the cataractous
25 human lens through a small surgical opening in the eye and the
26 replacement of the lens by a prosthetic intraocular lens placed
27 in situ. Biocompatible polymers presently or previously in use
28 are hyaluronic acid (Healon[™], Amvisc[™]); chondroitin sulfate, and

WO 95/07085

PCT/US94/10175

1 a combined solution of hyaluronic acid and chondroitin sulfate
2 (Viscoat™); and a hydroxypropylmethylcellulose solution
3 (Occucoat™). Research conducted recently demonstrates that
4 Healon™ and Amvisc™ are not surface active, but Viscoat™ and
5 Occucoat™ are.

6 Chondroitin sulfate does not exist as a free polysaccharide
7 in its native state, but as a proteoglycan. It is obtained from
8 sources associated with protein contaminants. The avoidance of
9 chondroitin sulfate avoids a potential source of pyrogenic
10 reaction, and the substantial cost associated with protein
11 removal.

12 Summary of the Invention

13 The invention presented herein discloses modified
14 mucopolysaccharide or viscoelastic solutions for use as
15 biologically active therapeutic infusions. In one form of the
16 invention, the mucopolysaccharide solution is formed from a
17 viscoelastic fraction and a buffer fraction. It has been found
18 that when a new synthetic molecule acyl-substituted hyaluronic
19 acid is employed as the viscoelastic fraction, control of
20 surface activity is achieved. An indicia of this is the
21 decrease of the surface tension of the solution which is now
22 within predetermined limits discussed below. Surface tension
23 modification is also accomplished with viscoelastic fractions in
24 which the acyl-substituted hyaluronic acid is mixed with one or
25 more of hyaluronic acid; and hydroxypropylmethylcellulose. In
26 certain applications, the viscoelastic solution of this
27 invention is used in a method of adhering a contact lens to the
28

WO 95/07085

PCT/US94/10175

1 surface of the eye, such as in association with procedures
2 permitting a medical professional to view ocular and intraocular
3 structures through the contact lens and through the viscoelastic
4 solution. This is particularly useful in facilitating surgical
5 procedures. In another application, the viscoelastic solution of
6 this invention is used by injection the solution into or under
7 structures or tissues within the eye, such as to dissect tissue
8 off of the retina.

9
10 In the broadest terms, surface active viscoelastic
11 solutions with controlled solution properties, are characterized
12 by surface tension, equilibrium contact angle, dynamic
13 viscosity, and cohesiveness (the measure of solution fracture
14 under stress). In a particular embodiment, this invention is
15 delimited by the three dimensional representation of Fig. 7.

16 In one example, bioengineered hyaluronic acid from a
17 bacterial source with an average molecular weight of 50,000 is
18 modified by acyl substitution with three to twenty carbon atom
19 acyl groups so that the resultant surface tension of such a
20 solution is between 40 and 65 dynes/cm². In the practice of
21 this invention, a viscoelastic solution having a surface tension
22 of less than about 56 dynes/cm², and more particularly, less
23 than about 50 dynes/cm² is of particular advantage.

24
25 This invention comprises a modified mucopolysaccharide
26 solution for use as a biologically active therapeutic infusion
27 comprising:
28

WO 95/07085

PCT/US94/10175

1 a pharmaceutical grade viscoelastic fraction selected from
2 the group consisting of acyl-substituted hyaluronic acid having
3 acyl groups thereof with three to twenty carbon atoms,
4 hyaluronic acid, hydroxypropylmethylcellulose and mixtures
5 thereof, and absent chondroitin sulfate said fraction having a
6 surface tension of between 40 and 65 dynes/cm²; and,

7 optionally with a physiological buffer fraction, such that
8 the viscoelastic comprises about a 0.1% percent of the solution
9 to about 5% of the solution, by weight, and preferably from
10 about 0.5 % to about 3%;

11 said modified mucopolysaccharide solution having a
12 viscosity of between 10,000 and 100,000 centipoise when measured
13 at a shear rate of 3 sec⁻¹ at 25°C; and,

14 optionally wherein the modified mucopolysaccharide
15 solution has a surface tension of less than about 56 dynes/cm²,
16 and further a surface tension of less than about 50 dynes/cm²;
17 and further,

18 optionally wherein the solution has an osmolality of from
19 about 250 to about 400 milliosmoles, or is generally isotonic
20 with ophthalmic tissue.

21 In some embodiments the modified mucopolysaccharide
22 solution viscoelastic fraction has an average molecular weight
23 of at least 50,000. Reference is further made to the
24 viscoelastic fraction being an acyl-substitute hyaluronic acid
25 having acyl groups thereof with three to twenty carbon atoms.

26 In particular applications the modified mucopolysaccharide
27 solution of this invention includes a surfactant fraction of a
28 biocompatible component selected from a group consisting of

WO 95/07085

PCT/US94/10175

1 phospholipids, monoglycerides, free fatty acids, free fatty acid
2 soaps, cholesterol, fluorocarbons, silicones, and nonionic
3 surfactants, with the surfactant present in an amount sufficient
4 to produce the required surface tension. In particular, a
5 biological surfactant fraction of a free fatty acid is present
6 in an amount of less than 1 mg/ml. Further embodiments include
7 a surfactant fraction of a biocompatible component selected from
8 a group consisting of phospholipids, monoglycerides, free fatty
9 acids, free fatty acid soaps, cholesterol, fluorocarbons,
10 silicones, and nonionic surfactants, said surfactant present in
11 an amount less than 10 micrograms/ml. In a preferred embodiment
12 the surfactant fraction of biocompatible component is a free
13 fatty acid.

14 In a further embodiment the modified mucopolysaccharide
15 solution has a viscoelastic fraction of a mixture of
16 acyl-substituted hyaluronic acid and hyaluronic acid, and
17 particularly with a surfactant fraction of a biocompatible
18 component selected from a group consisting of phospholipids,
19 monoglycerides, free fatty acids, free fatty acid soaps,
20 cholesterol, fluorocarbons, silicones, and nonionic surfactants,
21 with surfactant present in an amount sufficient to produce the
22 required surface tension, usefully in an amount less than
23 10 micrograms/ml. Preferred surfactants are free fatty acids
24 such as oleic acid.

25 Particular modified mucopolysaccharide solutions of the
26 invention are characterized by aspiration through a 0.3 mm
27 cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and
28 particularly in a range of 50 to 200 mm Hg, wherein the solution

WO 95/07085

PCT/US94/10175

1 is easily fractured. Similarly, those solutions with an
2 aspiration profile of from about horizontal up to about 1.5 and
3 more particularly from about horizontal to about 1.0 are
4 preferred.

5
6 In another embodiment this present invention comprises a
7 modified mucopolysaccharide solution for use during ophthalmic
8 surgery for protection of the internal ocular structures
9 including corneal endothelium from accidental touch by surgical
10 instruments, yet permitting of observation of said structures
11 comprising:

12 an optically clear polymeric fraction of high purity
13 mucopolysaccharides selected from the group consisting of
14 acyl-substituted hyaluronic acid having acyl groups thereof with
15 three to twenty carbon atoms, hyaluronic acid,
16 hydroxypropylmethylcellulose and mixtures thereof and absent
17 chondroitin sulfate, said fraction having a surface tension of
18 between 40 and 65 dynes/cm²; and,

19 optionally a physiological buffer fraction, such that the
20 viscoelastic comprises about a 0.1% percent of the solution to
21 about 5% of the solution, by weight, and preferably from about
22 0.5 % to about 3%;

23 said modified mucopolysaccharide solution having a
24 viscosity of between 10,000 and 100,000 centipoise when measured
25 at a shear rate of 3 sec⁻¹ at 25 C; and,

26 wherein said mucopolysaccharide fraction has an average
27 molecular weight of at least 50,000; and,

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WO 95/07085

PCT/US94/10175

1 a biological surfactant fraction of a free fatty acid
2 present in an amount less than 10 micrograms/ml; and,
3 optionally wherein the modified mucopolysaccharide
4 solution has a surface tension of less than about 56 dynes/cm²,
5 and further a surface tension of less than about 50 dynes/cm².

6 In some embodiment of this modified mucopolysaccharide
7 solution a particular polymeric fraction is hyaluronic acid.

8 Particular modified mucopolysaccharide solutions of the
9 invention are characterized by aspiration through a 0.3 mm
10 cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and
11 particularly in a range of 50 to 200 mm Hg, wherein the solution
12 is easily fractured, which optionally include those solutions
13 with an aspiration profile of from about horizontal up to about
14 1.5 and more particularly from about horizontal to about 1.0.

15 Another embodiment of the present invention includes a
16 pharmaceutically acceptable modified mucopolysaccharide solution
17 (particularly a surface active mucopolysaccharide) absent
18 chondroitin sulfate having a surface tension of between 40 and
19 65 dynes/cm²; and,

20 a viscosity of between 10,000 and 100,000 centipoise
21 (particularly an average molecular weight of at least 50,000)
22 when measured at a shear rate of 3 sec⁻¹ at 25 C.

23 optionally wherein the modified mucopolysaccharide
24 solution has a surface tension of less than about 56 dynes/cm²,
25 and further a surface tension of less than about 50 dynes/cm².

26 In this embodiment of a modified mucopolysaccharide
27 solution a particular polymeric fraction is hyaluronic acid.
28

WO 95/07085

PCT/US94/10175

1 In certain applications the mucopolysaccharide solution
2 further comprises a biological surfactant selected from a group
3 consisting of phospholipids, monoglycerides, free fatty acids,
4 free fatty acid soaps, cholesterol, fluorocarbons, silicones,
5 and nonionic surfactants.

6
7 Yet a further embodiment of the invention includes a method
8 of protecting internal ocular structures during ocular surgery
9 and retarding aspiration of material from the ocular surgery
10 site by the steps of:

11 intraocularly introducing biologically active therapeutic
12 infusion amount of a modified mucopolysaccharide solution
13 comprising:

14 a pharmaceutical grade viscoelastic fraction selected from
15 the group consisting of acyl-substituted hyaluronic acid having
16 acyl groups thereof with three to twenty carbon atoms,
17 hyaluronic acid, hydroxypropylmethylcellulose and mixtures
18 thereof and absent chondroitin sulfate, said fraction with a
19 surface tension of between 40 and 65 dynes/cm² (particularly
20 less than about 56 and more particularly less than about 50
21 dynes/cm²); and,

22 optionally a physiological buffer fraction, such that the
23 viscoelastic comprises about a 0.1% percent of the solution to
24 about 5% of the solution, by weight, and preferably from about
25 0.5 % to about 3%;

26 said modified mucopolysaccharide solution having a
27 viscosity of between 10,000 and 100,000 centipoise when measured
28 at a shear rate of 3 sec⁻¹ at 25 C. In such embodiment a

WO 95/07085

PCT/US94/10175

1 preferred method entails intraocularly introducing biologically
2 active therapeutic infusion amount of a modified
3 mucopolysaccharide solution by a syringe of about 1.13 cm³ in
4 cross section or less, and optionally about 0.57 cm³ or less,
5 and further optionally about 0.16 cm³. In certain embodiments a
6 "sloped" syringe absent sharp reductions in cross sectional area
7 is useful.

8 Further in this method the invention includes particular
9 modified mucopolysaccharide solutions characterized by
10 aspiration through a 0.3 mm cannula at a vacuum pressure in a
11 range of 5 to 400 mm Hg, and particularly in a range of 50 to
12 200 mm Hg, wherein the solution is easily fractured. Similarly,
13 those solutions with an aspiration profile of from about
14 horizontal up to about 1.5 and more particularly from about
15 horizontal to about 1.0 are preferred.

16
17 An additional embodiment of the invention includes a method
18 of protecting internal ocular structures during ocular surgery
19 by providing a viscoelastic solution that coats ocular
20 structures at a surgical site such that aspiration of the
21 viscoelastic solution is retarded, said method being:

22 intraocularly introducing biologically active therapeutic
23 infusion amount of a modified mucopolysaccharide solution absent
24 chondroitin sulfate and having a surface tension of between 40
25 and 65 dynes/cm² (particularly less than about 56 and more
26 particularly less than about 50 dynes/cm²); and,
27
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WO 95/07085

PCT/US94/10175

1 a viscosity of between 10,000 and 100,000 centipoise when
2 measured at a shear rate of 3 sec⁻¹ at 25 C. In such embodiment
3 a preferred method entails intraocularly introducing
4 biologically active therapeutic infusion amount of a modified
5 mucopolysaccharide solution by a syringe of about 1.13 cm³ in
6 cross section or less, and optionally about 0.57 cm³ or less,
7 and further optionally about 0.16 cm³.

8 Further in this method the invention includes particular
9 modified mucopolysaccharide solutions characterized by
10 aspiration through a 0.3 mm cannula at a vacuum pressure in a
11 range of 5 to 400 mm Hg, and particularly in a range of 50 to
12 200 mm Hg, wherein the solution is easily fractured. Similarly,
13 those solutions with an aspiration profile of from about
14 horizontal up to about 1.5 and more particularly from about
15 horizontal to about 1.0 are preferred.

16 A next method of the present invention includes a method of
17 protection of internal ocular structures including corneal
18 endothelium from accidental touch by surgical instruments, yet
19 permitting of observation of said structures comprising:

20 intraocularly introducing a modified mucopolysaccharide
21 solution during ophthalmic surgery wherein said solution
22 comprises

23 an optically clear polymeric fraction of high purity
24 mucopolysaccharides selected from the group consisting of
25 acyl-substituted hyaluronic acid having acyl groups thereof with
26 three to twenty carbon atoms, hyaluronic acid,
27 hydroxypropylmethylcellulose and mixtures thereof and absent
28

WO 95/07085

PCT/US94/10175

1 chondroitin sulfate, said fraction having a surface tension of
2 between 40 and 65 dynes/cm² (particularly less than about 56 and
3 more particularly less than about 50 dynes/cm²); and,

4 optionally a physiological buffer fraction, such that the
5 viscoelastic comprises about a 0.1% percent of the solution to
6 about 5% of the solution, by weight, and preferably from about
7 0.5 % to about 3%;

8 said modified mucopolysaccharide solution having a
9 viscosity of between 10,000 and 100,000 centipoise when measured
10 at a shear rate of 3 sec⁻¹ at 25 C; and,

11 wherein said mucopolysaccharide fraction has an average
12 molecular weight of at least 50,000; and,

13 a biological surfactant fraction of a free fatty acid
14 present in an amount less than 10 micrograms/ml.

15 In such embodiment a specific method entails intraocularly
16 introducing biologically active therapeutic infusion amount of a
17 modified mucopolysaccharide solution by a syringe of about 1.13
18 cm³ in cross section or less, and optionally about 0.57 cm³ or
19 less, and further optionally about 0.16 cm³.

20 Further in this method the invention includes particular
21 modified mucopolysaccharide solutions characterized by
22 aspiration through a 0.3 mm cannula at a vacuum pressure in a
23 range of 5 to 400 mm Hg, and particularly in a range of 50 to
24 200 mm Hg, wherein the solution is easily fractured. Similarly,
25 those solutions with an aspiration profile of from about
26 horizontal up to about 1.5 and more particularly from about
27 horizontal to about 1.0 are preferred.

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WO 95/07085

PCT/US94/10175

1 A next embodiment of the invention comprises a modified
2 mucopolysaccharide solution for use as a biologically active
3 therapeutic infusion comprising:

4 a pharmaceutical grade viscoelastic fraction selected from
5 the group consisting of acyl-substituted hyaluronic acid having
6 acyl groups thereof with three to twenty carbon atoms,
7 hyaluronic acid, hydroxypropylmethylcellulose and mixtures
8 thereof, and absent chondroitin sulfate said fraction having a
9 surface tension of between 40 and 65 dynes/cm² (particularly
10 less than about 56 and more particularly less than about 50
11 dynes/cm²); and,

12 said modified mucopolysaccharide solution having a
13 viscosity of between 10,000 and 100,000 centipoise when measured
14 at a shear rate of 3 sec⁻¹ at 25°C.

15 This invention encompasses a modified mucopolysaccharide
16 solution for use as a biologically active therapeutic infusion
17 comprising:

18 a pharmaceutical grade viscoelastic fraction selected from
19 a group consisting of an acyl-substituted hyaluronic acid having
20 acyl groups thereof with three to twenty carbon atoms and
21 mixtures of said acyl-substituted hyaluronic acid with
22 hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B,
23 chondroitin sulfate C, and hydroxypropylmethylcellulose, said
24 fraction with a surface tension of between 40 and 65 dynes/cm²;
25 particularly a viscoelastic fraction has an average molecular
26 weight of at least 50,000; and,
27
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WO 95/07085

PCT/US94/10175

1 optionally a physiological buffer fraction, such that the
2 viscoelastic comprises about a 0.1% percent of the solution to
3 about 5% of the solution, by weight, and preferably from about
4 0.5 % to about 3%;

5 whereby, upon infusion of modified mucopolysaccharide
6 solution at the site, the surface activity of the solution
7 enhances coating of the site.

8 A specific modified mucopolysaccharide solution is one with
9 an acyl-substituted hyaluronic acid, and a preferred viscosity
10 is between 10,000 and 100,000 centipoise when measured at a
11 shear rate of 3 sec^{-1} at 25°C , and optionally further including
12 a surfactant fraction of a biocompatible component selected from
13 a group consisting of phospholipids, monoglycerides, free fatty
14 acids, free fatty acid soaps, cholesterol, fluorocarbons,
15 silicones, and nonionic surfactants, said surfactant present in
16 a trace amount sufficient to produce said surface tension. In
17 one embodiment the surfactant is present in an amount less than
18 10 micrograms/ml. A preferred surfactant is oleic acid. A
19 preferred modified mucopolysaccharide solution comprises a
20 mixture of an acyl-substituted hyaluronic acid and hyaluronic
21 acid.

22 In a particular application this invention includes a
23 modified mucopolysaccharide solution for use a biologically
24 compatible therapeutic infusion comprising:

25 a pharmaceutical grade viscoelastic fraction selected from
26 a group consisting of hyaluronic acid, chondroitin sulfate A,
27 chondroitin sulfate B, and chondroitin sulfate C, said fraction
28 having an average molecular weight of at least 50,000.

WO 93/07085

PCT/US94/10175

1 a surfactant fraction of a biocompatible component selected
2 from a group consisting of phospholipids, monoglycerides, free
3 fatty acids, free fatty acid soaps, cholesterol, fluorocarbons,
4 silicones, and nonionic surfactants, said surfactant present in
5 a trace amount sufficient to produce a surface tension of
6 between 40 and 65 dynes/cm²; and,

7 optionally a physiological buffer fraction, such that the
8 viscoelastic comprises about a 0.1% percent of the solution to
9 about 5% of the solution, by weight, and preferably from about
10 0.5 % to about 3%;

11 whereby, upon infusion of modified mucopolysaccharide
12 solution at the site, the surface activity of the solution
13 enhances coating of the site and results in retardation of
14 aspiration at the site. A preferred modified mucopolysaccharide
15 solution has a viscoelastic fraction of hyaluronic acid, and,
16 optionally, a viscosity of between 10,000 and 100,000 centipoise
17 when measured at a shear rate of 3 sec⁻¹, and further
18 optionally, a surfactant, particularly oleic acid, and
19 particularly with surfactant present in an amount less than 10
20 micrograms/ml.

21 In one embodiment this invention includes a modified
22 mucopolysaccharide solution for use during ophthalmic surgery
23 for protection of the internal ocular structures comprising:

24 an optically clear polymeric fraction of high-purity
25 mucopolysaccharides and mixtures thereof, said polymeric
26 fraction selected from the group consisting of hyaluronic acid,
27 chondroitin sulfate A, chondroitin sulfate B, chondroitin

28